

# One-year outcome of patients submitted to routine fractional flow reserve assessment to determine the need for angioplasty

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## KEYWORDS

Coronary angioplasty;  
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**Aims** In patients submitted to coronary angiography, fractional flow reserve (FFR) assessment by a pressure wire can be used to guide the decision for revascularization. Routine application of FFR assessment and 1-year outcome of patients are poorly documented. The aim of this study was to report a 4-year single-centre experience where the use of FFR for decision making in equivocal lesions is encouraged.

**Methods and results** A prospective registry was designed to collect clinical and angiographic characteristics, as well as 1-year clinical follow-up for all patients submitted to FFR assessment. The decisional cut-off point for revascularization was 0.80. Over a 4-year period, out of 6415 coronary angiographies, FFR was measured in 407 (6.3%) patients (469 lesions). FFR was assessed through 4 or 5 Fr diagnostic catheters in 330 (81%). Median FFR value was 0.87 (0.80; 0.93). On the basis of FFR results, 271 (67%) patients were treated with medical therapy alone. A subset of 71 (17%) patients were not treated in accordance with the results of FFR. All patients but four (i.e. 99%) had 1-year clinical follow-up. Three hundred and forty four (85%) were free from clinical event, six (1.5%) patients died, five (4%) had an acute coronary syndrome, and 20 (5%) underwent target-vessel revascularization. Event-free survival was comparable in patients with vs. without revascularization ( $0.94 \pm 0.02$  and  $0.93 \pm 0.01$ , respectively). Patients had significantly better 1-year outcome when treated in accordance with the results of the FFR assessment.

**Conclusion** In routine practice, FFR assessment during diagnostic angiography was performed in 6.3%. On the basis of FFR, two-thirds of patients with 'intermediate' lesions were left unrevascularized, with a favourable outcome, when FFR was above 0.80. These data suggest that routine use of FFR during diagnostic catheterization is feasible, safe, and provide help to guide decision making.

## Introduction

In many clinical situations, coronary angiography is performed even when non-invasive tests are negative, doubtful, or not performed at all. When equivocal or intermediate lesions are observed, and in the absence of demonstrated ischaemia, decision making based on angiography alone is challenging.<sup>1,2</sup>

Pressure-derived fractional flow reserve (FFR) assessment has been extensively described and validated as a technique capable of identifying functionally significant lesions.<sup>3,4</sup> An FFR value below the threshold value of 0.75 corresponds to inducible ischaemia<sup>4,5</sup> and previous studies have shown that a strategy of revascularization based on FFR results in this context is acceptable.<sup>6,7</sup> This approach has previously been validated through a randomized study.<sup>7</sup>

The extension of FFR use to complex situations like multi-vessel disease,<sup>8</sup> serial lesions,<sup>9</sup> or after acute coronary

syndromes<sup>10,11</sup> has made this technique applicable in most clinical situations. In addition, the reliability of FFR measurement through 4 or 5 Fr diagnostic catheters has previously been demonstrated,<sup>12</sup> rendering this technique simple and convenient, and suitable for use in outpatients with reduced risk of vascular complication.<sup>13,14</sup>

However, despite these obvious advantages, FFR assessment remains under-used in routine practice, partially for financial reasons, but may be also because the long-term clinical outcome of routine practice patients is poorly documented. The aim of this study was to report a 4-year experience of routine FFR use, and the 1-year clinical outcome of the patients.

## Methods

### Study design

Patients were entered into a prospective, single-centre registry (from January 2000 to October 2003). All data were collected and controlled by a dedicated research team. Patients received

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written information about the study and gave their written informed consent. The study protocol was approved by the local Ethics Committee.

## Study population

All patients submitted to coronary angiography, for any reason, were eligible. In our centre, 4 or 5 Fr catheters were routinely used (Jogrophy, Jomed, Ulestraten, The Netherlands or Cordis Infinity, Cordis, Miami, FL, USA) and the decision to use FFR was left entirely at the operator's discretion. Nonetheless, all diagnostic angiographies were checked by at least two trained interventional cardiologists before the end of the procedure and typically FFR use was strongly encouraged in case of 'intermediate' angiographic stenosis (confirmed by a diameter stenosis  $>0.40$  and  $<0.60$  by quantitative coronary angiography (QCA) and no demonstrated myocardial ischaemia). FFR was also performed in case of positive non-invasive tests for ischaemia and 'non-significant' angiographic lesions ( $>20$  and  $<40\%$  diameter stenosis).

## FFR assessment technique

Coronary pressure was measured by a 0.014 sensor-typed pressure guide wire (Volcano Therapeutics Inc., Rancho Cordova, CA, USA) connected to a corresponding interface. Patients received 250 mg aspirin, 2500 IU heparin, and 0.2 mg nitroglycerine before the procedure. FFR measurements were performed according to standard practice.<sup>15</sup> After setting of the system and pressure calibration, the 0.014 in. pressure guide wire was placed distal to the lesion. If wire placement failed through a diagnostic catheter, then cross-over to a 7 Fr guiding catheter was recommended. The pressure gradient was recorded at baseline and after intracoronary injection of adenosine. The same dose of adenosine was used for both left and right coronary arteries, but the dose varied according to the recommended doses: in 2000, 20  $\mu\text{g}$ ;<sup>16</sup> 30  $\mu\text{g}$  in 2001 and 2002; and 60  $\mu\text{g}$  for the last 105 patients. FFR was automatically determined by the pressure console. The recorded FFR value was the average of at least two measurements. In patients not submitted to immediate angioplasty, the arterial sheath was removed immediately, the puncture site was manually compressed, and ambulation and discharge were allowed on the same day.

## Decision for revascularization, clinical events, and follow-up

On the basis of the specificity and sensitivity for detection of inducible ischaemia, the recommended decisional cut-off value for revascularization was 0.80. The study population was divided into two groups according to compliance with the FFR results: unrevascularized patients with  $\text{FFR} \geq 0.80$  and revascularized patients with  $\text{FFR} \leq 0.79$  formed the 'Compliance' group. Conversely, patients were assigned to the 'non-compliance' group when a decision for revascularization was made despite an FFR value  $\geq 0.80$  or when revascularization was deferred despite  $\text{FFR} \leq 0.79$ .

Clinical events were defined in the following order: death (all causes), occurrence of non-fatal acute coronary syndrome, and target-vessel revascularization. We did not take into account acute coronary syndrome related to a non-target vessel (demonstrated by both ECG and angiography). One-year clinical follow-up was obtained from hospital records, through direct or telephone contact with the patients, or by written correspondence with the referring physician.

## Statistical analysis

Categorical data are presented as number and percentage and continuous data as mean  $\pm$  1 standard deviation. Qualitative data were compared using the  $\chi^2$  test or with the likelihood  $\chi^2$  ratio test. Quantitative data were compared using the Student's *t*-test or the Mann and Whitney *U*-test where appropriate.

One-year survival was presented using Kaplan–Meier curves, comparisons were made using the Log-rank test, and 1-year event-free survival probability (standard error) has been calculated.

All tests were two-sided, a *P*-value  $<0.05$  was considered significant. Analyses were performed using SAS software, version 8 (SAS Institute Inc.).

## Results

### Baseline characteristics

From January 2000 to October 2003, out of 6288 patients submitted to coronary angiography, FFR was measured in 407 (6.5%) patients. The rate of use increased over time: 47/1566 (3%) in 2000, 99/1643 (6%) in 2001, 105/1509 (7%) in 2002, and 156/1570 (10%) in 2003 ( $P < 0.05$  for trend). In a majority of cases (81%), FFR was assessed through diagnostic catheters. Cross-over to a larger guiding catheter was required in 15%, and no reliable FFR value could be obtained in 4% of cases, either because of device failure or inadequate pressure guide placement. The only FFR-related complication was an occlusive dissection due to a plaque dissection by the pressure wire. This complication was not directly related to the use of a diagnostic catheter and was solved by crossing the occlusion with a regular guide wire followed by stent implantation.

The clinical and angiographic characteristics of the population and the results of the FFR measurements are presented in *Table 1*. In this population, 102 (25%) were diabetics and 26% presented with recent ( $<15$  days) acute coronary syndrome.

### Decision for revascularization

The decision to revascularize was made in 136 (33%), whereas 271 (67%) patients were left with medical therapy alone. There was no significant difference in clinical characteristics according to the decision for revascularization, except for a higher FFR value in the unrevascularized group ( $0.75 \pm 0.08$  vs.  $0.88 \pm 0.08$ ,  $P < 0.001$ ) and a non-significant trend for smaller minimal lumen diameter in the group with revascularization ( $0.97 \pm 0.04$  vs.  $1.12 \pm 0.05$ ,  $P = 0.08$ ). Discharge medical treatment was comparable in both groups, except in patients treated by angioplasty, who received Clopidogrel in addition to aspirin (for 1 month if they had stent implantation, and for 6 months in 12 patients treated with a drug-eluting stent in 2003).

### One-year outcome

All but four patients (i.e. 99%) had complete 1-year follow-up. During this period, six (1.5%) died, five (1.5%) had a non-fatal acute coronary syndrome, and 20 (5%) had target-vessel revascularization (*Figure 1*). In addition, 28 (6.7%) patients had revascularization of another vessel. There was no difference in the rate of clinical events between patients with and without revascularization (respectively, 9/136 (7%) vs. 22/271 (8%),  $P = 0.69$ ). Similarly, the 1-year event-free survival probability was comparable in both groups (respective probabilities =  $0.94 \pm 0.02$  vs.  $0.93 \pm 0.01$ ,  $P = 0.93$ ) (*Figure 2*).

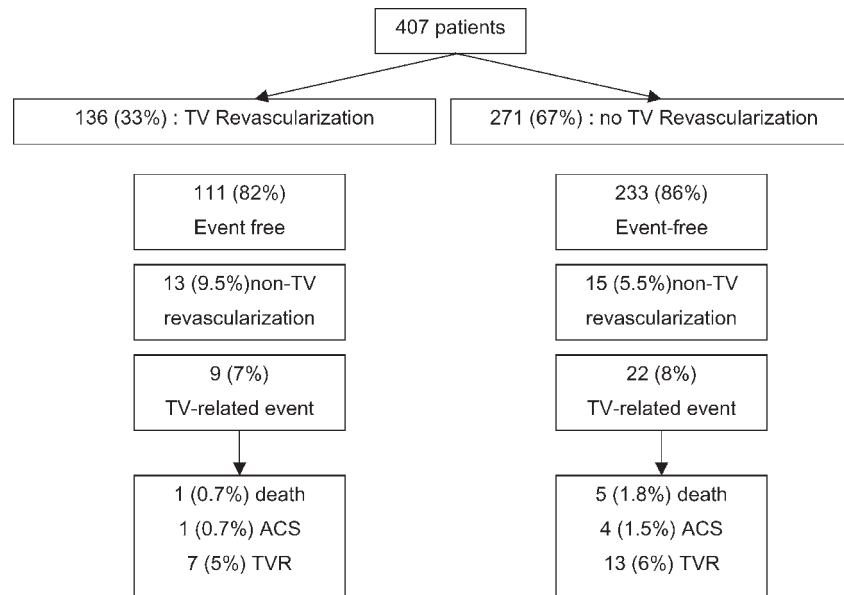
### Subgroups

Patients presenting with initial acute coronary syndromes represented 26% of the total population (105 patients,

**Table 1** Clinical and angiographic characteristics of the study population

	Overall (n = 407)	Revascularized patients (n = 136)	Unrevascularized patients (n = 271)	P-value
Male gender	278 (68%)	91 (67%)	187 (69%)	0.97
Age	59 ± 10	58 ± 11	60 ± 12	0.10
Acute coronary syndrome	105 (26%)	30 (22%)	75 (28%)	0.21
Risk factors				
High blood pressure	190 (47%)	69 (51%)	121 (45%)	0.55
Hypercholesterolaemia	290 (71%)	103 (76%)	187 (69%)	0.23
Smoker	251 (62%)	90 (66%)	161 (59%)	0.22
Diabetes	102 (25%)	33 (24%)	69 (25%)	0.91
Left ventricular ejection fraction	59 ± 12	58 ± 12	59 ± 9	0.70
Extent of coronary disease				
Single vessel	350 (86%)	113 (83%)	237 (87%)	0.72
Two vessel	50 (12%)	19 (14%)	31 (11%)	
Three vessel	7 (2%)	4 (3%)	3 (1%)	
Lesion site				
LAD	262 (64%)	93 (68%)	169 (62%)	0.65
LCx	58 (14%)	14 (10%)	44 (16%)	
RCA	82 (21%)	27 (20%)	55 (20%)	
LM	5 (1%)	2 (1%)	3 (1%)	
Reference diameter (mm)	2.70 ± 0.39	2.65 ± 0.61	2.82 ± 0.64	0.17
Minimal lumen diameter (mm)	1.07 ± 0.37	0.97 ± 0.41	1.12 ± 0.52	0.08
% Diameter stenosis	55 ± 12	57 ± 12	53 ± 16	0.12
FFR	0.85 ± 0.11	0.75 ± 0.08	0.88 ± 0.08	>0.01
FFR groups				
FFR ≤ 0.79	136 (33%)	102 (25%)	37 (9%)	
FFR ≥ 0.80	271 (67%)	34 (8%)	234 (57%)	

Comparison between revascularized and unrevascularized patients.

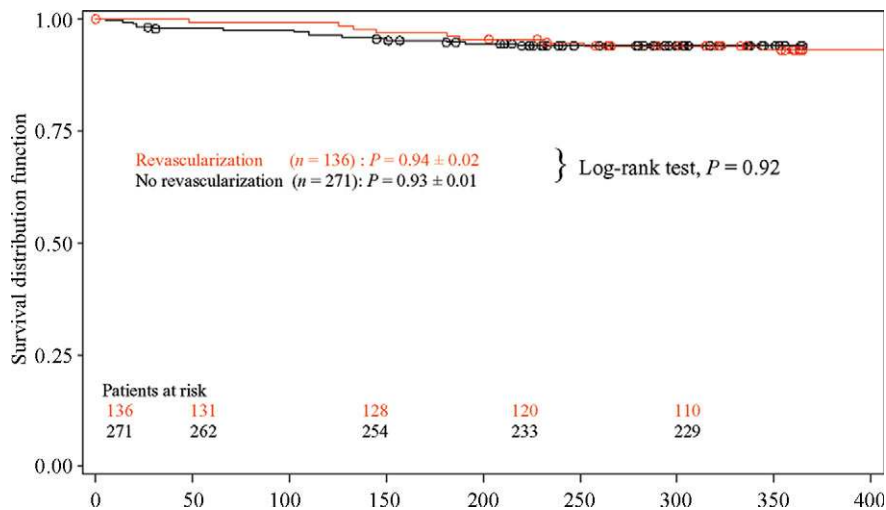


TV ; target vessel; ACS ; acute coronary syndrome; TVR ; target vessel revascularization.

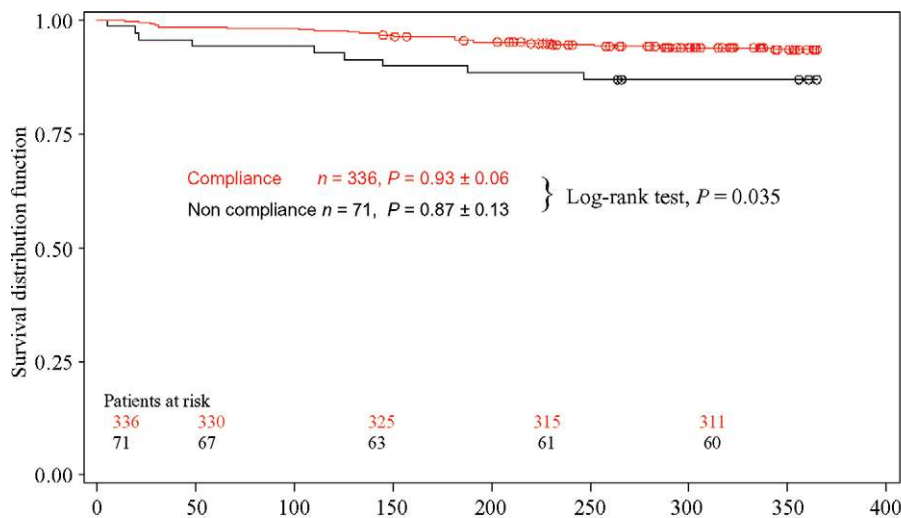
**Figure 1** Flow chart of the study population.

142 lesions). Among this group, 30/105 (26%) had initial revascularization (vs. 35% among non-ACS patients,  $P = 0.22$ ) and 10/105 (10.5%) had a target vessel-related clinical event (vs. 7% in non-ACS patients,  $P = 0.31$ ).

The compliance and non-compliance groups were defined retrospectively, comparing the results of FFR and the actual decision made. A decision in accordance with the FFR results was observed in 336 (83%) patients; 99 (24%) patients with



**Figure 2** 1-year event-free survival of patients submitted to revascularization vs. left under medical therapy alone (decision for revascularization based on pressure-derived FFR results).



Compliance group; unrevascularized patients with FFR  $\geq 0.80$  and revascularized patients with FFR  $\leq 0.79$ .  
Non-Compliance group; revascularization despite FFR  $\geq 0.80$  and no revascularization despite FFR  $\leq 0.79$ .

**Figure 3** 1-year event-free survival (without acute coronary syndrome or target vessel revascularization) in patients according to compliance with revascularization policy (decision to revascularize only if pressure-derived FFR  $< 0.80$ ).

FFR  $\leq 0.79$  submitted to revascularization and 237 (58%) patients with FFR  $\geq 0.80$  who were left with medical therapy alone. The non-compliance group comprised 71 (17%) patients; 34 (8%) with FFR  $\leq 0.79$  who had no revascularization and 37 (9%) with revascularization despite FFR  $\geq 0.80$ . No difference in risk factors was observed between the two groups; however, patients from the compliance group were older with smaller MLD, but less bifurcation lesions (29 vs. 40%,  $p = 0.10$ ). In the non-compliance group, 11/71 (15.5%) had an event vs. 20/336 (6%) in the compliance group ( $P = 0.01$ ). The characteristics of the two groups are presented in Table 2, the details of events in Table 3, and the event-free survival curves in Figure 3.

## Discussion

This study reports the largest cohort to date of consecutive patients treated according to the results of FFR

measurement in routine practice. Our results show that (1) this strategy was used in 6–10% of the whole population submitted to coronary angiography in a university centre, (2) FFR can be assessed safely through diagnostic catheters, (3) using a cut-off value of 0.80, one-third of the patients are submitted to revascularization, and (4) patients treated according to the results of FFR had favourable 1-year clinical outcome.

## Indication and rate of routine FFR use

Patients with 40–50% diameter stenosis by QCA, but without demonstrated ischaemia, represent a typical indication for FFR use to guide decision making. The clinical and angiographic characteristics of our population are broadly comparable with those reported in other observational<sup>17,18</sup> or randomized studies,<sup>7</sup> even though, in our study, we extended FFR use to patients with recent acute coronary

**Table 2** Clinical and angiographic characteristics of the patients treated in accordance with (compliance group) or not in accordance with (non-compliance group) the results of FFR

	Non compliance group (n = 71)	Compliance group (n = 336)	P-value
Male gender	48 (67%)	230 (68%)	0.97
Age	59 ± 15	62 ± 12	0.02
Risk factors			
High blood pressure	36 (51%)	145 (43%)	0.45
Hypercholesterolaemia	51 (72%)	239 (71%)	0.90
Smoker	43 (61%)	208 (62%)	0.84
Diabetes	13 (18%)	92 (27%)	0.11
Angiography			
Reference diameter (mm)	2.77 ± 0.62	2.65 ± 0.62	0.14
Minimal lumen diameter (mm)	1.20 ± 0.36	1.07 ± 0.36	0.02
% Diameter stenosis	56 ± 12	57 ± 16	0.55
Lesion site			
LAD	46 (65%)	214 (64%)	
RCA	13 (18%)	71 (19%)	
LCx	9 (13%)	49 (15%)	0.96
LM	3 (4%)	2 (0.6%)	
Bifurcation lesion	29 (40%)	98 (29%)	0.10
1-year clinical events	11 (15%)	20 (6%)	0.01

Compliance group and non-compliance group: definition as in Figure 3.

**Table 3** Clinical outcomes for patients treated in accordance with (Compliance group) or not in accordance with (non Compliance group) the results of FFR

	Non-compliance group (n = 71)		Compliance group (n = 336)	
	No revasc (n = 34)	Revasc (n = 37)	No revasc (n = 237)	Revasc (n = 99)
Clinical events	7/34 (21%)	4/37 (11%)	14/237 (7%)	6/99 (6%)
Death	2/34 (6%)	1/37 (3%)	3/237 (1%)	0/99
Acute coronary syndromes	2/34 (6%)	1/31 (3%)	2/237 (1%)	0/99
Vessel revascularization	3/34 (9%)	2/37 (5%)	9/237 (4%)	6/99 (6%)

Revasc, patients submitted to revascularization following the FFR assessment.

syndrome and multi-vessel disease. As a result, the routine use rate of FFR was 6.3% in the whole population submitted to diagnostic coronary angiography, with an increase over time from 3 to 10%. A similar rate and increase over time have been reported in another single centre experience.<sup>17</sup> In our centre, cost considerations were not a major concern, as neither the use of FFR nor the decision to revascularize had any direct economic impact for the patient or the medical team. Therefore, we can estimate that in a non-selected population and cost considerations aside, FFR use may be indicated in ~10% of routine coronary angiographies.

### Use of diagnostic catheters for FFR assessment and dose of IC adenosine

The reliability and safety of FFR assessment through diagnostic catheters have previously been demonstrated.<sup>12</sup> In the present study, FFR was assessed through 4 or 5 Fr diagnostic catheters in 80% of cases. The main interest of using diagnostic catheters is not to avoid arterial complications, but rather to make this technique as easy and

convenient as possible, minimize complexity, and to avoid the change in configuration for angioplasty. It is likely that the simplification of the FFR procedure has promoted its wider use in routine practice.

In our experience, only intracoronary adenosine was used, in order to make the procedure more simple. Previous studies have shown that a bolus of 18 µg is sufficient to induce complete hyperaemia.<sup>16</sup> Further studies have promoted the use of higher doses.<sup>19</sup> As no pullback manoeuvre was needed, we did not use the intravenous route.<sup>20</sup>

### FFR decisional cut-off value at 0.80 and clinical outcome

On the basis of sensitivity and specificity, the recommended cut-off value for FFR is 0.75,<sup>5,21</sup> and this threshold has previously been validated elsewhere in a randomized trial.<sup>7</sup> Nevertheless, an FFR cut-off value between 0.75 and 0.80 is usually considered to be in a 'grey zone'.<sup>22</sup> Extensive studies have demonstrated that FFR <0.75 indicates inducible ischaemia, whereas FFR >0.80 excludes ischaemia in 90%.<sup>23-27</sup> In our routine strategy, the choice of a threshold



at 0.80 aimed to give priority to the exclusion of ischaemia, at the risk of reduced specificity. In comparison with other reports, despite the higher FFR cut-off value (0.80 instead of 0.75), a similar (33%) revascularization rate was observed in our population.

We observed a similar 1-year event rate in both revascularized and non-revascularized patients. These results are in agreement with the DEFER study,<sup>7</sup> where there was no significant difference in late outcome between revascularized and non-revascularized patients with FFR >0.75. In our study, we observed a significantly better outcome in patients who were treated in compliance with FFR criteria, as compared to those who were not. Similar findings have been reported in a small series of 15 patients,<sup>8</sup> but the clinical outcome of patients left on medical therapy alone, despite an FFR below the threshold value, is poorly documented. [In the DEFER study, the 'non-compliant' ('perform') group was only composed of patients who were revascularized, despite an FFR above the threshold value]. Our data do not suggest any alternative explanation for the different evolution, as the compliance group patients had a similar risk profile to the non-compliance group (vascular risk factors, extent of coronary disease, initial presentation with acute coronary syndrome, left ventricular ejection fraction, or angiographic characteristics). In fact, they were older and had more severe lesions than those from non-compliance group.

### Study limitations

Despite the great attention paid to minimize bias, this study has several inherent limitations associated with cohort studies. Again, despite a clear indication for the use of FFR (intermediate lesions defined by on-line QCA measurements and lack of demonstrated ischaemia), other reasons may have influenced the decision to assess FFR. From our data, it is not possible to determine the relative impact of (1) the use of diagnostic catheters for FFR assessment, (2) the dose of adenosine used, (3) the extension of FFR indications to patients with unstable coronary syndromes, (4) the choice of the FFR threshold to guide the revascularization decision, and (5) the potential bias in FFR measurement due to conductance problems, especially in the case of diffuse arterial disease.

### Conclusions

Routine use of FFR to guide revascularization strategy was indicated in 407 patients (6.3% of all coronary angiographies) and was performed through diagnostic catheters in most cases. Using a cut-off value of 0.80, the indication for revascularization was limited to one-third of all patients. One-year clinical follow-up demonstrated that patients left with medical treatment alone had a similar outcome to those submitted to revascularization. In conclusion, the subset of patients in whom the decision to revascularize contradicted the FFR results had less favourable event-free survival. These data suggest that routine use of FFR during diagnostic catheterization is feasible, safe, and provide help to guide decision making.

**Conflict of interest:** no author has any conflict of interest to declare.

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## Clinical vignette

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### Repair of all the components of the syndrome of aortic regurgitation and VSD

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There is still no agreement about the need for, timing, and type of repair of the Syndrome of VSD and AR (syndrome of Laubry and Pezzi). The syndrome is commonly thought of as due to a simple prolapse of the aortic leaflet into a 'high' VSD. We believe that the syndrome is caused by congenital discontinuity of the media of the aortic sinus from the crest of the interventricular septum. This results in aneurismal dilatation and bulging of the right coronary sinus into the RVOT, VSD, and prolapse of the aortic cusp. Images in this report illustrate all the anatomical components both before and after repair using a simple technique described previously by us.

Panel A. The discontinuity between the aortic media and the crest of the septum, the longitudinal dilatation of the sinus of Valsava, the prolapse of the cusp, and lack of coaptation of the aortic cusps. This was associated with moderate aortic regurgitation with a jet directed towards the anterior mitral leaflet (Panel C). During systole, the VSD shunt is apparent (Panel E), while in diastole the dilated sinus and prolapsing cusp obstruct the VSD (Panel C). Following simple transaortic repair, re-attachment of the crest of the septum to the aortic media results in closure of the VSD, correction of the dilated sinus, elevation of the aortic cusp with increased coaptation (Panel B), and marked improvement in AR, which become 'trivial' (Panel D). There were no shunts detected during systole (Panel F) or diastole (Panel D).

